Remarks

Claims 1, 2, 6-65, and 80-85 are pending in the application. Claims 1, 2, 6-20, 23-25, 27, 28, 30, 37, 46-65, and 80-85 stand rejected, and claims 21, 22, 26, 29, 31-36, and 38-45 have been withdrawn from consideration. Claims 1, 2, 6, 46, 63, 82, 83, 84, and 85 are amended as above. No new claims have been added. No new matter is added to the Specification by these changes. Applicant respectfully requests reexamination and reconsideration of the case, as amended. Each of the rejections levied in the Office Action is addressed individually below.

I. Rejection under 35 U.S.C. § 102(b), as being anticipated by Moynihan. Claims 63 and 64 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Moynihan (U.S. Patent 5,589,189). The Examiner maintains that since liposomes are microparticles and microparticles are solid according to the Applicant's previously submitted argument regarding the previous rejection under 35 U.S.C. § 112, first paragraph, claims 63 and 64 are anticipated by Moynihan. The Examiner has misunderstood the Applicant's argument regarding the previous rejection under § 112, first paragraph. The microparticles used in claims 63 and 64 are *not liposomes*; therefore, Moynihan cannot anticipate the claimed invention.

Present claims 63 and 64 recite "solid" microparticles. The Applicant argued previously that solid microparticles are not liposomes. Some liposomes are in fact microparticles due to their size, but they are not solid microparticles as recited in the claimed invention. Lipsomes are fluid filled vesicles surround by a layer or multiple layers of lipid. Since liposomes have a liquid core and a fluid, lipid layer surrounding the liquid core, the liposomes are not solid. At column 1, lines 55-57, Moynihan states in the "Background of the Invention" that "liposomes are microscopic vesicles made from phospholipids, which form closed, fluid filled spheres." In contrast, the microparticles used in claims 63 and 64 are solid microparticles. The microparticles of the claimed invention were further described in the previously submitted arguments under § 112, first paragraph (see Response under 37 C.F.R. § 1.111, filed July 13, 2004). Given the methods described for making the inventive particles (*e.g.*, spray drying, single and double emulsion solvent evaporation, solvent extraction), the scanning electron micrograph of the particles (see Figure 1 of the application), and the description that the agent to be delivered is encapsulated by a lipid-protein-sugar matrix (see the "Summary of the Invention"), it is clear that

the inventive microparticles are not liposomes. Therefore, it is clear from the claims themselves and from the claims read in light of the specification that the inventive microparticles do not include liposomes. Even though it is clear from the specification as originally filed and pending claims that the microparticles used in claims 63 and 64 are not liposomes but are instead solid microparticles, the Applicant has added the phrase "wherein the microparticles are not liposomes" to independent claim 63 in order to further prosecution. Since Moynihan only teaches liposomes and does not teach solid microparticles, Moynihan cannot anticipate the claimed invention. Applicant, therefore, requests that the rejection be removed.

Furthermore, the microparticles used in the claimed method include a lipid-protein-sugar matrix. To the extent that the material described by Moynihan can be said to include a "matrix" and an "agent," as recited in the present claims, the "matrix" element would be the lipid layer of Moynihan's liposomes. Thus, Moynihan's material does not have a lipid-protein-sugar matrix. The "agent" in Moynihan's composition would be hemoglobin, albumin, and sugar, which are in the core of the liposomes. These components are not in the matrix. Therefore, the liposomes taught by Moynihan do not meet all the limitations of the claimed invention because they do not include a lipid-protein-sugar matrix. Moynihan can not anticipate the claimed invention without teaching all limitations of the claims; therefore, Applicant requests that the rejection be removed.

II. Rejection under 35 U.S.C. § 102(a), as being anticipated by Bot *et al.* (U.S. Patent 6,423,345). Claims 1, 2, 6, 7, 13, 17-20, 23-25, 27, 28, 30, 37, 46, 48-53, 57-60, 62-65, and 80-85 remain rejected under 35 U.S.C. § 102(a) as being anticipated by Bot *et al.* (WO 00/00215). The Examiner states that the Declaration of Dr. Kohane submitted with the last Response is not commensurate with the scope of the claims. The Examiner continues that the claims are broader in scope than the Declaration because Exhibit B of the Declaration only describes encapsulating nifedipine and bupivacaine. Applicant respectfully disagrees as one of ordinary skill in the art reading the evidence presented in Exhibit B would understand that any agent, and particularly any small molecule drug, could be encapsulated in a lipid-protein-sugar particle. Therefore, the Declaration of Dr. Kohane as previously filed does support the full breadth of the claims.

The evidence presented with the Declaration supports the pending claims reciting a solid microparticle of an agent encapsulated in a matrix comprising lipid, protein, and sugar. The

calcium channel blocker nifedipine and the anesthetic bupivacaine were only exemplary agents to be incorporated into lipid-protein-sugar particles. It should be noted that these two agents are from two different classes of drugs and furthermore that these two agents have different chemical structures. They merely represent two examples of agents which can be encapsulated in the inventive particles. Demonstration that these agents could be incorporated into the particles established that other agents including other drugs, proteins, peptides, nucleic acids, *etc.* could also be encapsulated in a lipid-protein-sugar microparticle. Therefore, the Declaration is evidence that the claimed invention was made before January 6, 2000, and the Bot reference should be removed as prior art against the present application. Applicant respectfully requests that the rejection be removed.

III. Rejection under 35 U.S.C. § 103(a), as being unpatentable over Moynihan (U.S. Patent 5,589,189). Claims 1, 2, 6, 7, 13, 16, 18-20, 23-25, 27, 28, 30, 37, 46, and 57-61 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Moynihan (U.S. Patent 5,589,189). The Examiner maintains that since liposomes are microparticles and the Applicant has argued that microparticles are solid, then liposomes are solid. As discussed above, this is an incorrect understanding of the Applicant's previously presented argument. Liposomes are not solid microparticles; therefore, Moynihan, which only teaches liposomes, cannot render the claimed invention obvious.

The pending claims of the present application recite solid microparticles. Although liposomes are microparticles, they are not solid. In the Remarks section of the previously filed Response, Applicant was merely pointing out that the term "microparticle" as used in the claims referred to solid microparticles. The description, photomicrographs of the inventive microparticles, and methods of making the microparticles support this use of the term "microparticles" in the claims. Liposomes are fluid-filled vesicles surrounded by a layer of lipid. Rather than being solid, liposomes are substantially fluid-like. Therefore, Moynihan which only teaches liposomes can not render the claimed invention obvious.

In addition, in order to make the distinction between the inventive microparticles and liposomes clearer, Applicant has added the clause "wherein the microparticles are not

liposomes" to each of the rejected independent claims. Applicant respectfully requests that the rejection be removed.

Furthermore, as discussed above, the claimed particles include a lipid-protein-sugar matrix which the liposomes taught by Moynihan do not have. Therefore, Moynihan does not teach all the limitations of the claims and cannot alone render the claimed invention obvious.

IV. Rejection under 35 U.S.C. § 103(a), as being unpatentable over Bernstein *et al.* (U.S. Patent 6,423,345). Claims 1, 2, 6, 7, 12-20, 23-25, 27, 28, 30, 37, 46-65, and 80-85 maintains the rejection under 35 U.S.C. 103(a) as being unpatentable over Bernstein *et al.* (U.S. Patent 6,423,345). Examiner states that since Berstein discloses a drug delivery composition that comprises a polysaccharide and a lipid or a protein and a lipid, a third composition can be formed from a combination of the two compositions. The Examiner continues citing *In re Kerkhoven* for the proposition that the "idea of combining them flows logically from their having been individually taught in the prior art." Applicant disagrees.

The idea of picking and choosing particular components to come up with the claimed microparticles does not logically flow from Bernstein. The Examiner is invited to more specifically explain how a microparticle with a matrix consisting of three components such as a lipid, sugar, and protein logically flows from Bernstein. Changing the composition of the matrix changes the properties of the matrix. In Bernstein, for example, a lipid is integrated into the polymeric matrix to alter drug release kinetics. Altering the components of the matrix alters the adhesive properties of the matrix. It was not until the inventive particles were made and tested that it was known such particles could be formed, would be stable, and would be useful in the drug delivery arts. As pointed out in the last Response, an important aspect of the claimed invention is the recognition that various combinations of proteins, sugars, lipids, and synthetic polymers can be used to formulate microparticles useful in the drug delivery arts. If the Examiner wishes to maintain this rejection, the Applicant requests that the Examiner point out particularly the suggestion or teaching of such a composition, and why preparing such a composition would reasonably succeed in creating microparticles for drug delivery. Without such a showing a *prima facie* case of obviousness has not been demonstrated.

With respect to claims 6, 82, and 83, the claims have been amended as the Examiner suggested to exclude lipids from the matrix of the particles. Applicant submits that the amended claims are not rendered obvious by Bernstein because all the drug delivery compositions of Bernstein include a lipid. Bernstein cannot render obvious a microparticle which excludes lipids from the matrix.

V. **Rejection under 35 U.S.C. § 103(a), as being unpatentable over Bernstein *et al.* (U.S. Patent 6,423,345) and further in view of Goldenheim *et al.* (U.S. Patent 6,534,081).** Claims 8-11 remain rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over Bernstein *et al.* (U.S. Patent 6,423,345), and further in view of Goldenheim *et al.* (U.S. Patent 6,534,081). As discussed above, Bernstein does not render obvious the matrix comprising at least three components selected from the group consisting of lipids, proteins, sugars, and synthetic polymers. Therefore, even if there is a teaching or suggestion to combine Goldenheim and Bernstein, the combination would not render the claimed invention of claims 8-11 obvious because the combination still does not teach a matrix comprising at least three components selected from the group consisting of lipids, proteins, sugars, and synthetic polymers. Applicant respectfully requests that the rejection be removed.

VI. **Rejection under 35 U.S.C. § 103(a), as being unpatentable over Bot *et al.* (WO 00/00215).** Claims 47, 54-56, and 61 stand rejected by the Examiner under 35 U.S.C. § 103(a), as being unpatentable over Bot *et al.* (WO 00/00215). As discussed above, the Bot *et al.* reference has been removed from consideration as a prior art reference under 35 U.S.C. § 102(a) by the Declaration submitted by Dr. Kohane previously. Applicant submits that the Declaration is evidence that the invention as claimed was conceived before the publication of Bot. The Declaration taken in the context of the art is commensurate with the scope of the claims because other agents besides nifedipine and bupivacaine could be incorporated into the inventive microparticles. Applicant, therefore, requests that this rejection be removed.

VII. Rejection under 35 U.S.C. § 103(a), as being unpatentable over Bot *et al.* (WO 00/00215) in view of Goldenheim *et al.* (US Patent 6,534,081). Claims 8-11 stand rejected under 35 U.S.C. § 103(a), as being unpatentable over Bot *et al.* (WO 00/00215) in view of Goldenheim *et al.* (US Patent 6,534,081). As discussed above, the Bot *et al.* reference has been removed as a prior art under 35 U.S.C. § 102(a) by the Declaration submitted with the last Response. Without the teachings of Bot *et al.*, the Examiner has not established a *prima facie* case of obviousness; therefore, Applicant requests that the rejection be removed.

In view of the forgoing amendments and arguments, Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

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